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MELATONIN, LIGHT AND CIRCADIAN CYCLES

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SUMMARY

The body's circadian rhythms affect many aspects of human psychology, physiology, and performance. Melatonin, a hormone secreted by the pineal, is an important element of human circadian rhythmicity. Melatonin is normally at a low level during the day, with a pulse of secretion at night. The timing of melatonin secretion is controlled by the suprachiasmatic nuclei of the hypothalamus. The neuronal pathways which mediate this control are discussed.

Light exposure is the main factor which adjusts the hypothalamic clock that controls melatonin release. Melatonin is altered in many disease states. It interacts with other endocrine systems. It probably plays a role in jet lag.

Various drugs, including many that are commonly used and are likely to be taken by military personnel, can affect the melatonin system at different levels: by shifting the hypothalamic clock which controls melatonin release; by directly suppressing release at the level of the pineal, without altering the underlying rhythm; or by altering or blocking the effects of melatonin after it has been released. Performance implications of military personnel taking such drugs are unknown. Significant effects would be most likely under circumstances where circadian rhythmicities are likely to have an impact, such as sustained operations, night work and travel across multiple time zones.

The details of the light/dark melatonin relationship in humans need to be better defined. Investigation into using various interventions (drugs, light/dark stimuli, exercise, etc.) to adjust circadian rhythmicity could produce military applications.

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Introduction

The purpose of this paper is to provide United States Navy research and medical personnel with a review of scientific information on melatonin. Effects of light on melatonin and other circadian variants are discussed, and various drugs which alter blood levels or effects of melatonin are addressed. There is an operational need to better understand the physiological and performance effects of circadian rhythms. It is also important to understand effects of commonly used medications and to determine whether drug products or physiological interventions can be used to improve performance and mission readiness. Circadian rhythms remain a major factor in performance degradation during sustained military operations, or when travel is required across time zones. The hormone melatonin is an important regulator of neural and endocrine processes involved in synchronization of circadian rhythms. Light affects circadian rhythms mostly via melatonin. Controlled light exposure and pharmacological agents which can affect circadian rhythms could be valuable to the operational community and need to be investigated.

Chemistry and Secretion

Melatonin, N-acetyl-5-methoxytryptamine, was discovered in 1958 by Lerner and associates (Lerner et al., 1958). It is a methoxyindole hormone synthesized primarily in the pineal, with a half-life of 10 to 40 minutes (Levy, 1983a). The synthesis is diagrammed in Figure 1. Serotonin (5-hydroxytryptamine) is synthesized in two steps from the amino acid tryptophan which is ingested as a component of dietary protein. Protein-calorie malnutrition decreases serum melatonin levels in rats and it is conceivable that ingestion of large quantities of tryptophan could affect melatonin levels (Herbert and Reiter, 1981). The conversion of serotonin to N-acetylserotonin by the enzyme N-acetyltransferase (NAT) is the rate limiting step in synthesis of melatonin (Klein et al., 1970; Klein and Weller, 1970). Melatonin is not stored, but is released soon after synthesis, and 70% is bound to plasma albumin (Miles and Philbrick, 1987). It is extremely lipid soluble and therefore widely distributed in the body (Wurtman, 1986). Melatonin is present in numerous areas of the brain, with high affinity

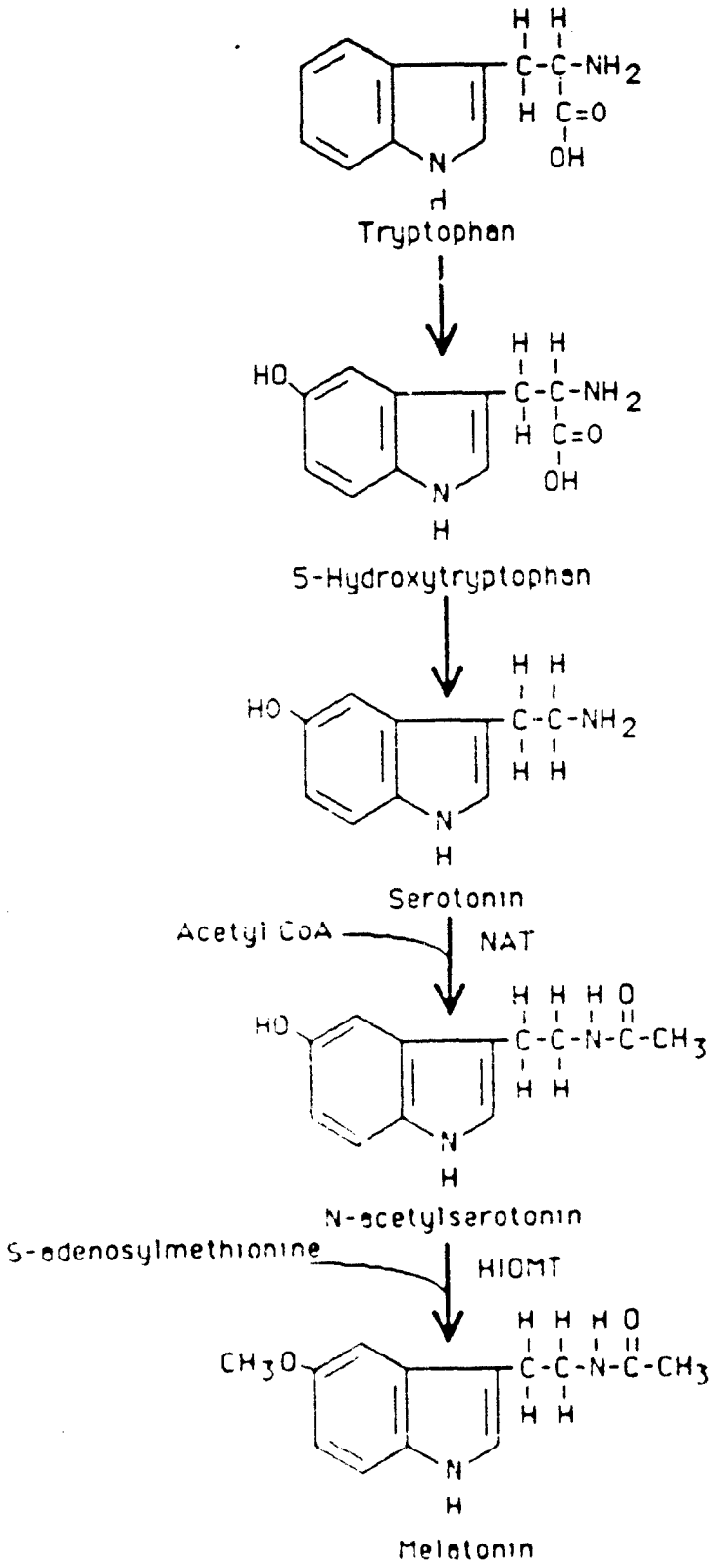

Figure 1 Melatonin Synthesis

binding in the hippocampus, striatum and hypothalamus (Vanecek et al., 1987). Some of melatonin's metabolites show biologic activity and thus may be responsible for part of melatonin's effects (Dubocovich, 1988). Degradation involves hepatic microsomal 6-hydroxylation to 6-hydroxymelatonin which is conjugated to sulfate and excreted in the urine (Miles and Philbrick, 1987). Catabolism may be different in the brain.

Plasma melatonin levels are low during the day with a pulse of secretion during the night. This is true in all mammals, including those which are active predominantly at night. Melatonin levels in urine (Lynch et al., 1975) and cerebrospinal fluid and levels of melatonin metabolites in plasma and urine show similar patterns (Reiter, 1986). Salivary and serum levels of melatonin are highly correlated ($r=.8$, $p<.001$, Novak et al., 1987), and salivary levels are about 30% of plasma levels (Vakkuri, 1985). Plasma, urinary, and salivary 24 hour patterns are quite constant in a given individual over time, but there is significant variation between individuals (Claustrat et al., 1986; Bojkovski et al., 1987b; Miles et al., 1987). These levels can be determined accurately by radioimmunoassays (Bojkovski et al., 1987b; Nowak et al., 1987; Skene, 1987).

The circadian temperature curve shows the reverse pattern of melatonin, with high temperatures during the day and low at night. The negative correlation between melatonin and body temperature persists during sleep deprivation (Åkerstedt et al., 1979). The two rhythms are not quite 180° out of phase, with the peak of melatonin occurring 2 to 4 hours before the temperature trough. Since there is evidence that melatonin lowers body temperature (Ralph et al., 1979) this may be a causal relationship. Figure 2 shows melatonin and (reversed) temperature curves for 12 healthy young men at baseline and during sleep deprivation.

Illnerová et al., (1985) reported the onset of the melatonin pulse in humans occurs later in winter than summer. Animal studies demonstrate longer melatonin pulses in winter or with longer dark periods (Reiter, 1986). A similar pattern is reported in humans (Kuappila et al., 1987), however, data are not consistent (Illnerová et al., 1985; Reiter, 1986). Melatonin secretion may be under genetic control (Wetterberg et al., 1983). For example,

Japanese women appear to have lower melatonin levels than North-American whites of mixed ethnic origin (Wetterberg et al., 1978).

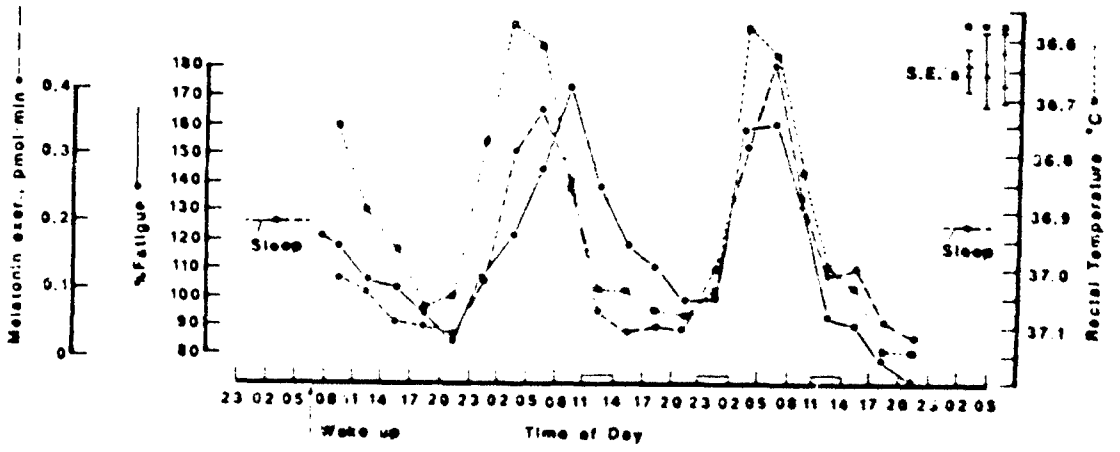

Figure 2. Melatonin in urine, self-rated fatigue (linear trend removed), and reversed body temperature in 12 subjects over 64 hr of sleep deprivation. Akerstedt et al., 1979.

Melatonin and Age

Looking at melatonin levels through life, mean nocturnal melatonin levels are initially very low. They increase to a peak of about ≈130 pg/mL between

ages one to three. They drop steeply between that peak and ages 15-20 with levels correlating inversely with body weight and body surface area (Iguchi et al., 1982; Waldhauser et al., 1988). Thereafter, there is a gradual decline into old age and the association between body size and melatonin levels is probably lost (Nair et al., 1986a; Touitou et al., 1986; Waldhauser et al., 1988; Sharma et al., 1989), although Arendt et al., (1982) suggest that the relationship with body size persists. There may be a small decrease in daytime serum melatonin levels with age. However, the predominant change is marked decrease in the nocturnal pulse. Older subjects also show an increased lag from sunset to onset of the melatonin pulse (Nair et al., 1986a; Nair et al., 1986b) and to peak pulse (Sharma et al., 1989). So the pulse starts later, peaks lower and later, and ends sooner. These age related changes are exaggerated in subjects with Alzheimer's disease (Nair et al., 1986b).

Males and females have similar melatonin levels through most of life; however, elderly women average higher levels than elderly men (Iguchi et al., 1982; Touitou et al., 1986). In rats aging is associated with decreased density of melatonin receptors in the hypothalamus (Zisapel, 1988). It has been hypothesized that decreased melatonin with age plays a causal role in many detrimental changes of aging (Rozencvaig et al., 1987), and that melatonin may have youth preserving properties (Pierpaoli and Maestroni, 1987).

The Melatonin Control System

Figure 3 shows structures and humoral factors involved in melatonin release. In mammals the circadian pattern of melatonin release is controlled by an oscillator in the suprachiasmatic nucleus of the hypothalamus (SCN). (The control system in birds differs. The pineal of the chick shows an independent circadian cycle, without hypothalamic input. Zatz and Mullen, 1988.) A mutant form of golden hamster has an oscillator with a cycle of about 20 hours instead of 24, controlled by a single autosomal locus, with heterozygous animals showing intermediate cycle lengths (Ralph and Menaker, 1988). Transplantation of the SCN from an animal of the mutant variety to a normal

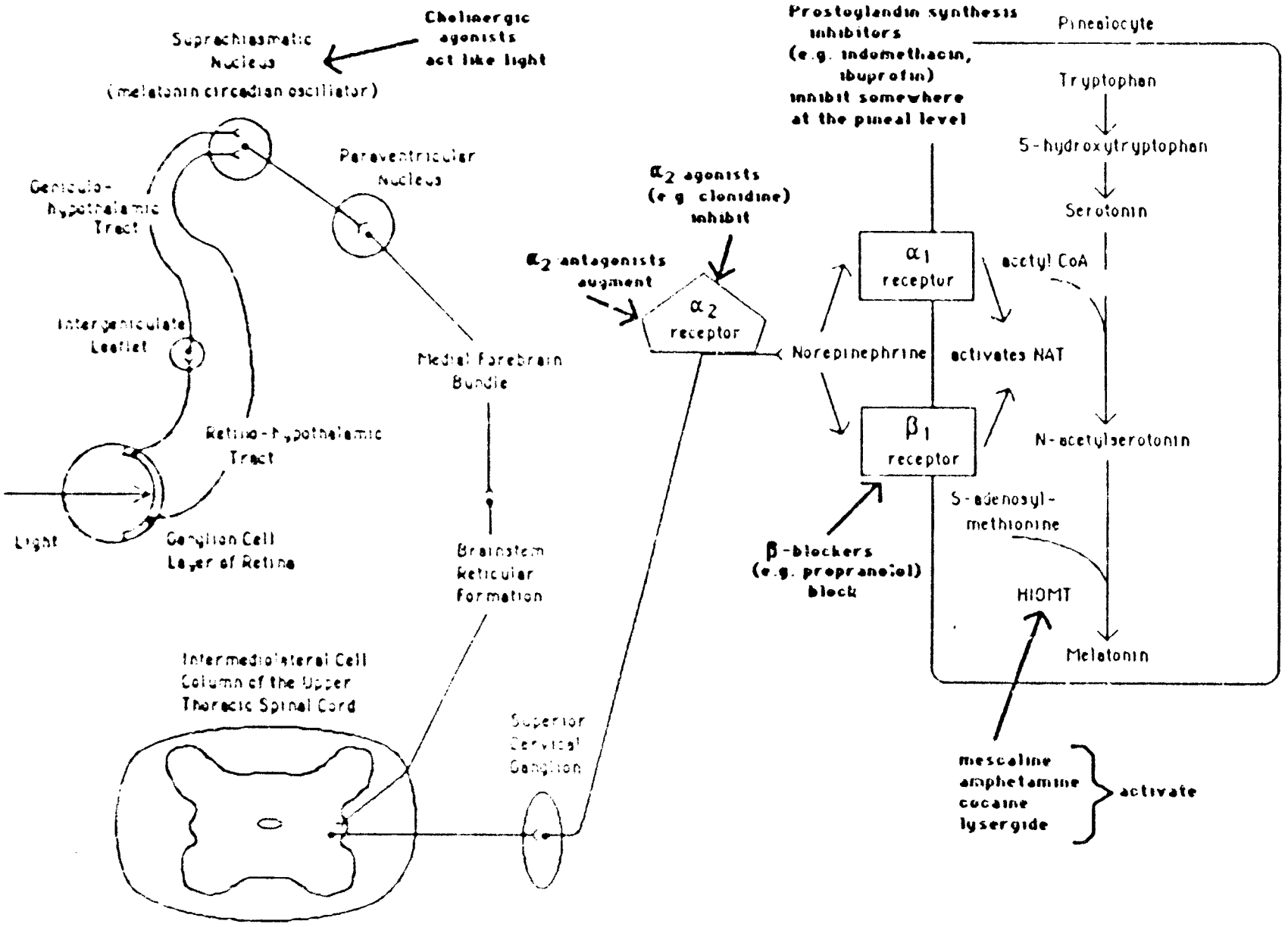

Figure 3 The Melatonin Control System

animal converts the endogenous circadian cycle of the recipient to that of the donor (Ralph et al., 1988).

The primary natural synchronizer of the hypothalamic oscillator is light. All vertebrates, other than mammals, have extraretinal photoreceptor input to the circadian system. In mammals the only significant photoreceptor input appears to be from the retina (Nelson and Zucker, 1981; Yanovski et al., 1986). Although, apparently, sufficient natural light can penetrate the skull in mammals to stimulate photoelectric cells in the brain tissue, and it has been suggested that this could play a slight role in blind individuals (Zacharias and Wurtman, 1964). However, there is no evidence that this is the case.

Information passes from cells in the ganglion cell layer of the retina to the SCN directly via the retino-hypothalamic tract and indirectly via the intergeniculate leaflet (IGL) and then the geniculo-hypothalamic tract. The optic tracts involved in vision are not required for melatonin control (Moore and Klein, 1974; Sadun et al., 1984; Harrington and Rusak, 1986; Pickard et al., 1987). Visual SCN neurons of rat and hamster respond to retinal illumination with a sustained increase (most) or a sustained decrease in electrical discharge in a dose response pattern to light intensity (Meijer et al., 1986). Another study in hamsters found the predominant response was increased regularity in firing of previously irregular neurons. The response to a given light stimulus was affected by the light pattern the animal was accustomed to (Stoughton et al., 1987). The SCN has projections to the paraventricular nucleus of the hypothalamus (PVN) which has projections to the intermediolateral cell column of the spinal cord, where preganglionic cell bodies have projections to the superior cervical ganglion (SCG), from which postganglionic fibers run to the pituitary in the conarian nerve (Ebadi and Govitrapong, 1986).

At night, when there is no light, the sympathetic nerve terminals from the SCG release more norepinephrine in the pineal. This stimulates post-synaptic beta$_1$adrenoreceptors and (in some animals including man) to a lesser degree alpha$_1$adrenoreceptors on the surface of the pinealocytes, causing cyclic AMP synthesis which induces activity of the rate limiting

enzyme NAT by a process involving RNA and protein synthesis (Axelrod, 1974). Prostaglandins may be involved in enzyme induction (Surrall et al., 1987). If input from SCG to pineal is blocked, enzyme activity remains at its low daytime level. Effects of norepinephrine released by SCG postganglionic fibers can be blocked by propranolol (a beta-adrenergic receptor antagonist). Sympathetic nerves in the pineal have a standard negative feedback mechanism mediated by presynaptic alpha$_2$-adrenoreceptors. Stimulation of these receptors inhibits norepinephrine (and thereby melatonin) release (Pelayo, et al., 1977; Levy et al., 1986; Grasby et al., 1988).

Blocking caudal output from the suprachiasmatic nucleus has similar effects to light exposure (Zatz and Brownstein, 1979). Stimulation of the suprachiasmatic nucleus with the cholinergic agonist carbachol (by injecting it into the ventricular system of the brain) mimics the effect of light (Zatz and Brownstein, 1979; Earnest and Turek, 1985), suggesting a cholinergic mechanism of transmission. Injection of the excitatory amino acid glutamate into the SCN of free running (constant light or constant dark) hamsters caused a phase shift of the activity rhythm, suggesting that this chemical also may be involved in melatonin control (Meijer et al., 1988). Lesions of the PVN, the next step in the pathway, eliminate the increased NAT activity and melatonin production in the pineal at night. Electrical stimulation of the PVN during the early part of the day (or lights-on period) in rats elevates urinary melatonin metabolite output (Yanovski et al., 1986).

Thus it appears that information about light goes from retina to SCN, from there to the PVN, and then via the intermediolateral cell column to the SCG. During the dark phase of the circadian cycle, SCG neurons release more norepinephrine into the pineal. Norepinephrine leads to activation of NAT, stimulating melatonin synthesis and release. Light exposure inhibits this pathway. Rabbits and primates, including man, may also have parasympathetic innervation to the pineal. However, no functional role for this innervation has been established (Moore, 1978).

Aside from the pineal, small amounts of melatonin are produced in the retina. It has been proposed that melatonin may alter the pigment aggregation in the retina and thus change the eye's light sensitivity and perhaps

the ability of light to affect circadian rhythms (Miles and Philbrick, 1988). It is possible that non-pineal sources of melatonin may explain the persistence of some circadian effects of light after pinealectomy (Ellis et al., 1982). The melatonin production of the hamster retina increases substantially after pinealectomy (Steinlechner et al., 1987).

Light, Darkness, Melatonin and Circadian Rhythms

Light is the main affector of melatonin synthesis. The system is not so simple as 'light turns it off, dark turns it on'. Light has different effects depending on when it is administered. Its effects can vary depending on the subject's recent light exposure. Those accustomed to different ratios of light and dark, to constant light, or to constant darkness may respond quite differently to the same stimulus.

Pulses of darkness have circadian effects in animals. Exposing hamsters who have been living under constant light conditions to periods of darkness can affect the circadian cycle of physical activity (Boulos and Rusak, 1982; Ellis et al., 1982; Harrington and Rusak, 1986), but this does not necessarily imply melatonin effects. Light blocks melatonin production very quickly, however, NAT induction after sympathetic stimulation requires one to two hours, (Lewy, 1983a). Therefore, if dark pulses can affect melatonin, the darkness interval would have to exceed two hours to demonstrate the effect. We have found no studies of effects of darkness on melatonin synthesis or release in humans. Vaughan et al., (1976) and Weinberg et al., (1979) reported that having subjects sleep during the usual light period did not cause an increase in melatonin. However, lights were on during sleep in those studies.

In addition to directly suppressing melatonin levels, light exposure can also adjust the hypothalamic oscillator so that there is a persistent phase shift in the cycle of melatonin release. A "phase shift" means that the secretion curve moves in relation to time of day. For example, if a person's peak (maximum) melatonin level occurred at 0500 each morning and some stimulus caused a 2 hour phase advance then his peak would occur at 0300. A 2 hour phase delay would move it to 0700. Stimulation of the SCN

with carbachol, which simulates the effects of light can also cause such shifts. Agents such as beta blockers, which act at the level of the pineal to acutely change melatonin, do not cause persistent phase shifts.

Light has been shown to have circadian effects in all animals tested (excluding blind animals). When the phase of the melatonin cycle is shifted by light exposure or interventions that act at the hypothalamic level (e.g. carbachol), other circadian rhythms (temperature, hormones, activity) generally shift with it. However, since other circadian rhythms are quite sensitive to "zeitgibers" (time cues) other than light, while melatonin is less so (Lewy and Sack, 1989), dysynchronies may occur if all zeitgibers do not correspond. For example, if light/dark is shifted but sleep/wake is held constant.

Since shifts in onset and offset of the melatonin pulse and other circadian rhythms in response to light intervention are not always parallel, it has been suggested that 2 coupled controlling oscillators may be involved (Illnerová and Vanecek, 1982; Honma et al., 1985; Illnerová and Vanecek, 1987). Others feel one oscillator can explain patterns of melatonin release (Lewy and Sack, 1989). Another question is whether different circadian variants are controlled by different oscillators as is suggested by the fact that under some circumstances subjects show different phase lengths for different rhythms (e.g. activity and temperature, Kronauer et al., 1982). Fuller et al., (1981) reported that destruction of the SCN in squirrel monkeys obliterated circadian rhythms of drinking, behavioral activity, and feeding but that temperature rhythm persisted, indicating at least one other circadian oscillator. Unfortunately, melatonin was not measured in that study.

Time of Day Interaction with Light Effects

Light has different effects at different times of day and night. Early morning light tends to advance the onset of the melatonin pulse and time of spontaneous awakening, while evening light delays the pulse (Arendt and

Broadway, 1987; Lewy et al., 1987; Dijk et al., 1989). Studies demonstrating shifting the melatonin cycle with light will be discussed in the section on Light Therapy for Depression.

Other circadian rhythms appear to be affected similarly. Czeisler et al., (1989) demonstrated that the temperature rhythm was maximally delayed by light exposure just before the circadian low of body temperature and maximally advanced by exposure right after the circadian low. As you move further from the temperature minimum, there is less and less effect. An approximate phase response curve for humans adapted from that report is illustrated in Figure 4. The curve shows a remarkable similarity to the

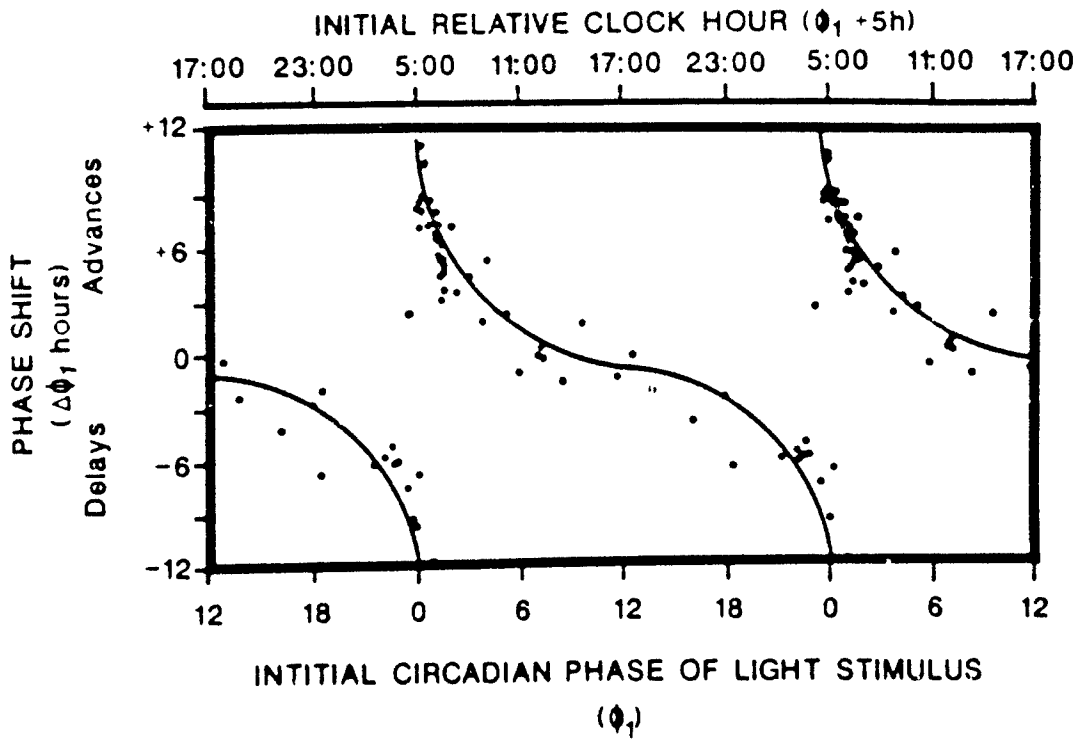

Figure 4: Phase shift vs initial circadian phase of light stimulus. (Adapted with permission from Figure 5 in Czeisler et al., Science, Vol. 244, pages 1328-133, 16 June 1989. Copyright 1989 by the AAAS.)

phase response curves of many other animals (see review by Pittendrigh, 1988). This is a response curve for body temperature; unfortunately, melatonin itself was not measured in that study. Also, it must be kept in mind that this study involved 3 nights of light pulses in conjunction with a sleep phase shift.

Czeisler et al., (1989) emphasize the importance of other light exposure during the same circadian cycle as a bright light stimulus. Even quite dim light, depending on its timing and duration, can change effects of a given bright light stimulus. Studies in insects and mammals showing that additive phase shifts can be accomplished by 2 sequential light stimuli in the same circadian period support this finding (Pittendrigh, 1988).

Czeisler et al., (1989) also demonstrated the importance of timing light stimulus relative to an individual's own circadian cycle. The times of maximum phase advances and delays are very closely located on either side of the circadian low, so a slight shift in timing of the midpoint of the weighted average of light exposure (bright plus dim) in relation to an individual's temperature curve could change the effect from a large phase delay to a large phase advance or vice versa. As temperature curves can vary considerably between persons, establishment of the temperature curve before attempting large phase shifts would appear essential. Thus, recommendations to seek out bright light exposure at anytime during daylight hours after crossing time zones (Ehret and Scanlon, 1983) might be counterproductive.

Large delays in circadian rhythms are more quickly accomplished in rats than large advances (Illnerová et al., 1987). However, Czeisler et al., (1989) showed a symmetric phase response pattern in humans, with advances apparently as easy to accomplish as delays, at least for body temperature (see Figure 4). Very short pulses of light during the dark period can affect circadian rhythms in some animals (Hoffmann, 1982, Illnerová and Vanecek, 1982). Indeed, short pulses sometimes seem as effective as longer exposures (Illnerová et al., 1979). Studies in humans describe some acute melatonin suppression within 30 minutes (Arendt, 1988). However, we have not found reports of persistent phase shifts with such short stimuli.

Although many light exposure studies involve sleep deprivation because of early morning light treatments, sleep deprivation alone does not cause the melatonin suppression. In fact, sleep deprivation without bright light exposure appears to elevate melatonin levels (Åkerstedt et al., 1979; Salín-Pascual et al., 1988). We have found no reports of effects of bright light exposure during sleep deprivation.

Light and Circadian Duration

It appears that light and other zeitgebers are constantly working to entrain our circadian rhythms to the 24 hour cycle. When human subjects are isolated from all cues as to time of day, their circadian rhythms tend to cycle at about 25 hours (Wever, 1986; Roelfsema, 1987). When a subject's circadian rhythms are independent of the actual time of day like this, they are said to "free run". Blind subjects may show melatonin curves that are phase advanced or phase delayed with respect to the light/dark and wake/sleep cycles, or they may free run as isolated non-blind subjects do. When they free run, the sleep/wake cycle remains entrained to the 24 hour light/dark cycle by social factors and relationships between these cycles and the melatonin cycle are constantly changing (Levy and Newsome, 1983). Blinded rats also have been reported to show a free-running pattern (Moore and Klein, 1974).

In normal subjects who have been converted to a free running pattern, light and other zeitgebers can entrain circadian rhythms to periods longer or shorter than 24 hours. Depending on the timing and intensity of light, rhythms can be prolonged or shortened. Using the range of periods to which human subjects can be entrained as a measure of light's strength as a zeitgeber, bright light seems to be stronger than any other factor that has been studied, allowing entrainment to cycles as short as 18 or as long as 30 hours (Wever et al., 1983; Polaski and Wever, 1986; Wever, 1986). This could have implications for the non-24 hour shift work cycles sometimes used on ships and in other military environments. Adjusting the length of the circadian cycle could allow workers to maintain a more constant relationship between their work/rest, wake/sleep cycles and their internal biologic rhythms, which might improve mood, sleep quality or performance.

Light Intensity

Light of very low intensity can affect melatonin in some animals (e.g. rats, Thiele et al., 1983) but not humans (Lewy, 1983b). Whether dim light will suppress melatonin depends in part on the brightness level the animal is habituated to. Animals accustomed to bright light during day will not show melatonin suppression with dim light exposure, while animals who have only been exposed to dim light will (Lynch et al., 1981). Studies of the natural pattern of light exposure have shown many people are exposed to daylight intensities a very small portion of the day, with some subjects experiencing intensities of 1,000 lux or more for less than 1 hour per day (Okudaira et al, 1983, Savides et al., 1986; Campbell et al., 1988). Despite this, humans must be exposed to very bright light to get any effects on melatonin. When broad spectrum light (most commonly Vita-Lite fluorescent light) is used, there is increasing effect with increased intensity. Most human studies have used light in the 2000 to 3000 lux range, although some go much higher (Lewy et al., 1980; Czeisler et al., 1986; Strassman et al., 1987). Partial melatonin suppression, however, was reported with 300 lux (100 $\mu W/cm^2$) light administered to human subjects for 30 minutes at midnight (Bojkowski et al., 1987a).

It probably takes more light to shift the melatonin curve than to suppress melatonin acutely. Terman et al., (1989) showed a phase shifting response to fairly dim light (max 1000 lux) in humans. In that study light was administered to sleeping patients for 7 to 14 days. The light was turned on gradually over several hours, simulating the normal pattern of dawn light in spring. It was maintained at dawn intensity until patients awakened (usually within a few minutes). The melatonin pulse was reported to be "clearly advanced". However, the study did not include a control group, and these results are in contrast to most other reports where effects on body rhythms by light/dark cycles using light less than 1500 lux were used. In these studies the responses were minimal unless light treatment was combined with other zeitgebers or the dark portion of the cycle was made absolutely dark, thereby forcing a rest period at that time, which serves as a social zeitgeber (Czeisler et al., 1981; Wever, 1980). While dim light alone is relatively ineffective for adjusting the human pacemaker, changing the

timing of an 11 hour exposure to light of 150 lux can reverse the direction of phase shifting effects from 5 hours bright light (10,000 lux) administered during the same circadian cycle (Czeisler et al., 1989).

Wavelength of Light

The light intensity required for melatonin entrainment in the hamster has been shown to depend on the wavelength, with maximum sensitivity at around 500 nm (Takahashi et al., 1984; Brainard et al., 1986). A study in humans suggested a similar wavelength. Using monochromatic light, that study also showed a clear dose response curve for light intensity and amount of suppression of melatonin. The threshold for suppression was markedly less than that reported for effects with white light exposure (Brainard et al., 1988). As subjects in that study had their pupils kept at maximum dilation with a long acting midriatic agent, it probably underestimates the intensity required under usual light exposure circumstances when the pupil constricts. However, it is likely that light in this spectral range would be effective at an intensity lower than other color spectra of light. The report by Czeisler et al., (1989) showing that phase shifts can be predicted using a "brightness-weighted average" of light exposure suggests that light effects are proportional to duration times intensity, that the same effects could be achieved with different intensities of a given type of light by varying duration of treatment appropriately.

Circadian Rhythms and Jet Lag

Disruption of melatonin and other circadian cycles probably contributes to jet lag. Salivary melatonin measurements in one subject showed a gradual obliteration of the normal circadian pattern after an eastward flight, with subsequent development of a pattern appropriate to the new time zone. There was preservation of the usual curve, with gradual shifting to the new position after a westward flight (Nowak, 1988). Following time zone changes different circadian rhythms (e.g. temperature, heart rate, sleepiness) may shift by varying amounts so that the individual has internal dysynchronization along with being out of phase with external time (Wegmann et al., 1986). Performance measures appear to follow the circadian temperature

curve during adaptation to a phase shift (Wilkinson, 1982). The temperature curve is often blunted after a transmeridian flight. Likewise, performance curves also tend to be blunted, with subjects never reaching their baseline peak performance nor falling to their baseline low (Gundel and Wegmann, 1989).

Some studies have found bright light treatment to be beneficial in jet lag (Daan and Levy, 1984; Czeisler and Allen, 1987), and a possible commercial device to facilitate its use to prevent jet lag is being developed (Kripke and Cole, 1989). Light therapy could have applications for preventing jet lag in troops required to perform missions shortly after crossing multiple time zones. If effects relate to adjustment of melatonin secretion pattern, then light might also help persons required to work other than the usual daytime shift.

Light Exposure and Sleep

Bright light treatment has been reported to have only mild effects on sleep. Changes that have been reported include both increases and decreases in rapid eye movement (REM) sleep time (Saletu et al., 1986; Dijk et al., 1989), shortened or lengthened REM latency (Levy et al., 1984; Sack et al., 1986; Dietzel et al., 1986), and improved sleep maintenance and subjective sleep quality (Lingjærde et al., 1985; Dietzel et al., 1986; Saletu et al., 1986; Hansen et al., 1987). Sleep effects of bright light may vary depending on the population tested. For example, Skverer et al. (1988) reported that bright light treatment increased the amount and percent of delta sleep and the sleep efficiency of seasonal affective disorder patients but had the reverse effect in normal subjects.

Interestingly, subjects tended to feel sleepy during 3 or 6 hour exposures to 5000 lux light and often actually fell asleep (Honma and Honma, 1987). It has been suggested that the decreased exposure to natural bright light that occurs in the elderly may be causally related to the decreased sleep quality also seen in that group (Campbell et al., 1988). It might be interesting to determine whether elderly persons with cataracts had more sleep problems than those without.

It is not clear that bright light effects on sleep relate to light induced changes in melatonin. Claustrat et al. (1986) found no relationship between the occurrence of plasma peaks and troughs of melatonin and stages of sleep through the night. However, some changes have been reported in sleep EEG distribution during melatonin administration (Hishikava et al., 1969; Young and Silman, 1981), and Antón-Tay et al. (1971) reported increased alpha activity in awake subjects given melatonin.

Melatonin and Affect

There appears to be a relationship between melatonin and mood. Much of melatonin research in humans has involved depressed patients. Such patients (particularly severely depressed patients) show a lower evening rise in serum melatonin and a lower mean melatonin level than normals (Nair et al., 1984). However, Claustrat et al. (1984) reported that the melatonin circadian curves depressed patients were not abnormally phase shifted. Some studies have found increased melatonin with successful treatment of the depression while others have not (Mendlewicz et al., 1979; Mendlewicz et al., 1980; Wetterberg et al., 1979 and 1982; Claustrat et al., 1984; Brown et al., 1985; Hariharasubramanian et al., 1986; Stevart and Halbreich, 1989). Carman et al. (1976) found that giving melatonin to depressed patients caused increased depression.

There is some preliminary data that manic depressive patients may have elevated melatonin levels, particularly early in the manic phase with much reduced levels when depressed. There also have been reports of abnormal circadian secretion patterns, with the phase of the curve being advanced more in mania than during depression (Miles and Philbrick, 1988). One study found that the drop in nighttime plasma melatonin levels with light exposure was greater in manic-depressive patients than in normals, both when they were acutely ill and during periods of affect. Such supersensitivity may be a trait marker for bipolar affective disorder (Levy et al., 1985).

Melatonin and Antidepressant Drugs

How such melatonin abnormalities may relate to mechanisms of action of antidepressant drugs is not clear (Smith et al., 1979; Miles and Philbrick, 1988; Checkley and Palazidou, 1988). The tricyclic antidepressants (e.g. desmethylimipramine, desipramine, imipramine) which inhibit norepinephrine uptake (giving the effect of more norepinephrine release) acutely exaggerate the increased pineal cAMP synthesis produced by catecholamines and thereby increase melatonin. Chronic use of such drugs may alter number and sensitivity of adrenergic receptors (Checkley and Palazidou, 1988; Miles and Philbrick, 1988). Some human studies have shown persistent elevations of plasma melatonin with tricylcics, others have not. Effects may differ between normal and depressed subjects (Checkley and Palazidou, 1988).

Monoamine oxidase is one of the main enzymes involved in catabolism of catecholamines. Blocking this enzyme increases available norepinephrine just as blocking reuptake does. The monoamine oxidase (MAO) inhibitor antidepressant tranylcyromine (non-selective) and clorgyline (selective, MAO-A) elevate melatonin both acutely and chronically in humans, while the fairly selective MAO-B type inhibiter, deprenyl, does not (Murphy et al., 1986). MAO-A and MAO-B are present in the brain in about equal amounts (Baldessarini, 1985), however, the noradrenergic fibers in the pineal apparently contain mostly MAO-A (Checkley and Palazidou, 1988). An alternative possibility is that antidepressants may alter the retina's light sensitivity (Terman, 1988).

Light Therapy for Depression

Bright light has been used as therapy in typical depression, with variable success (Kripke et al., 1983a, 1983b, 1986). However, much more work has been done in seasonal affective disorder (SAD). SAD is a cyclic illness with recurrent fall/winter depressed episodes fulfilling major affective disorder criteria, alternating with spring/summer euthymia or hypomania. It is more common at higher latitudes in the U.S. and tends to be relieved by traveling South. Patients frequently manifest "atypical" depressive features as well as daytime drowsiness and carbohydrate craving. SAD

typically begins in the second or third decade of life, is four times as common in women as men, is associated with abnormal sleep patterns, and may be related genetically to other forms of affective illness (Rosenthal et al., 1984). As approximately 20%-25% of normals complain of moderate to marked changes in mood and energy across the seasons, findings from studies on SAD patients may have application to a broad population (Jacobsen et al., 1987a; Terman, 1988)

There have been many recent studies attempting to treat SAD with exposure to bright light at various points in the circadian cycle, usually morning and/or evening. Most studies have shown some benefit within a few days, with morning light perhaps being more effective than evening exposure (Rosenthal et al., 1984 and 1985; James et al., 1985; Hellekson et al., 1986; Byerley et al., 1987; Levy et al.. 1987; Terman, 1988). It appears that subgroups of SAD patients may respond to either only morning or only evening light (Rosenthal et al., 1988). More than 30 minutes of morning light seems to be necessary for benefit (Wirz-Justice et al., 1987), and increasing duration (at least up to 2 or 3 hours) and/or brightness is probably associated with increasing benefit (Rosenthal et al., 1988). There is evidence that childhood cases are also helped by bright therapy (Rosenthal et al., 1986a). Full spectrum light is not necessary for reversal, as incadescent light (Jacobsen et al., 1987a) and fluorescent light of limited spectrum (Rosenthal et al., 1988), have both been found beneficial. Most reports have found light must be bright for benefit. However, Wirz-Justice et al. (1986) describe benefits with dim light as well and Terman et al. (1989) used low intensity light administered gradually in a normal dawn pattern during sleep, showing evidence of relieving SAD and of shifting the melatonin pulse.

The mechanism of light benefits in SAD is not firmly established. The data are conflicting. The finding that phototherapy to the eye is more effective than to the skin (Wehr et al., 1987b) supports the possibility that melatonin is involved. Some researchers believe that light adjusts an abnormally shifted melatonin circadian curve. Levy et al. (1987) found SAD patients showed delayed melatonin onset times and altered phase response curves. Levey et al. (1988) found a high correlation between delay in

melatonin onset and degree of depression in a group of 14 SAD patients, and Partonen et al. (1989) found that beneficial one hour morning bright light treatment in SAD patients advanced the melatonin acrophase by one to two hours. Skwerer et al. (1988) reported low nocturnal melatonin secretion in SAD patients similar to that seen in typical depressives. Skwerer et al. (1988) report that basal plasma norepinephrine levels in SAD patients are related inversely to degree of depression and that norepinephrine levels increased after successful bright light therapy. However, increased plasma levels of norepinephrine don't prove that more norepinephrine is being released in the pineal where it would affect melatonin.

Not all evidence is consistent with a melatonin mechanism for light benefits in depression. Jacobson et al. (1987a) and Wehr et al. (1986) reported that melatonin profiles in SAD patients were normal. Jacobson et al. (1987b) found that bright full spectrum light given in the early afternoon was as effective an SAD treatment as early morning light. Because midday light is not expected to cause a phase shift in the melatonin cycle (see Figure 4, note that the curve is almost flat between 1200 and 2200 o'clock, indicating little response to light in this period). Benefits from light exposure at this time of day suggests a non-melatonin antidepressant mechanism. Wehr et al. (1986) found that administering 3 hours of light in late morning and early afternoon was as effective in relieving SAD as the same amount of light in the early morning and late evening, even though only the latter affected melatonin. They also found that oral administration of melatonin failed to increase depression scores in patients who had responded to phototherapy. Rosenthal et al. (1986b) also report some cases in which melatonin did not increase depression but others where melatonin did reverse light effects on depression. Wehr et al. (1986) and Rosenthal et al. (1988) reported that atenolol (a beta-adrenergic receptor agonist which inhibits the production of melatonin) did not differ from placebo in its antidepressant effectiveness in patients with SAD.

Circadian Cycles and Depression

The varying results discussed above may relate to the heterogeneity of depressive illness. Lewy et al. (1988) have theorized that there are a

variety of circadian types in depression, some phase advanced and some delayed. They also propose two additive effects for light in depression, one based on phase shifting and the other on "energizing". To discriminate such effects, studies need to document baseline and post treatment temperature cycles and, if possible, the melatonin cycle. The existence of SAD type patients whose depression occurs in summer rather than winter (Wehr et al., 1987a) emphasizes the heterogeneity of these affective disorders and the likelihood that different mechanisms underlie symptoms in different people.

Melatonin and Schizophrenia

There have been variable reports as to melatonin levels and circadian patterns in schizophrenia (Ferrier et al., 1982a and 1982b; Wetterberg et al., 1982; Fanget et al., 1989). Melatonin is structurally related to a number of psychomimetic agents, and it has been theorized that abnormal melatonin metabolism in schizophrenics might generate psychoactive products and contribute to the symptoms. At present there is no convincing evidence that this is the case or that melatonin plays a significant role in schizophrenia (Miles and Grey, 1988; Miles and Philbrick, 1988).

Melatonin and Immunity

Acute stress suppresses the immune system, causing cortical atrophy and decreased weight of the thymus gland in mice. Melatonin also affects the immune system (Maestroni et al., 1988). If melatonin is administered to stressed mice who have been antigen primed, it prevents loss of thymus weight, not by preventing the cortical atrophy, but by causing hypertrophy of the medulla, presumably by acting on antigen-activated mature T-cells. Stress atrophy is thought to be due to adrenal steroids triggered by stress related release of adrenocorticotropic hormone (ACTH). Exogenous corticosterone causes similar atrophy, and this too is blocked by melatonin (again, only in antigen primed animals). Stressed antigen-primed mice injected with doses of a virus which would be sublethal without stress die. If similarly treated mice are also injected with melatonin they show normal (non-

stressed) survival rates. Melatonin increases antibody production but does not enlarge the thymus of antigen primed non-stressed mice.

These immune augmenting effects of melatonin are blocked by the mu-type opiate receptor blocker naltrexone, but not by the delta-type opiate receptor blocker ICI 174,864, suggesting that melatonin activates or causes release of endogenous opiate peptides which in turn bind to mu or kappa-type opiate receptors and counter the effect of stress and/or corticosterone in antigen primed animals (Maestroni et al., 1988). The relationship is complex. For example, melatonin appears to reduce plasma levels of beta-endorphins (Lissoni et al., 1984), while it seems to enhance some other endogenous opiates (Kumar et al., 1982).

Melatonin and Cancer

Perhaps related to its immune system effects, melatonin impacts on various tumors. Lack of melatonin (pinealectomy) stimulates some tumor growth but may inhibit others. This area was revieved recently by Blask and Hill (1988). Melatonin administration has been reported to stimulate, inhibit or have no effect on growth of various tumors depending when in the circadian cycle it is given and/or on the dose level used. For example, in the MCF-7 variety of human breast cancer, physiological (but not supra- or subphysiological) concentrations of melatonin inhibit *in vitro* cell growth, and the effects of melatonin *in vivo* and *in vitro* interact with those of estrogen and/or prolactin (Blask and Hill, 1986; Sánchez-Barceló et al., 1986). *In vitro* studies suggest that melatonin effects on estrogen-responsive human breast cancer involves an interaction with estradiol receptors (Blask and Hill, 1988).

Changing the light/dark cycle can alter melatonin effects on cancer. Also, light alone can affect tumors. For example, rats with a type of carcinoma show decreased tumor growth and increased survival under constant dark as compared to constant light (Blask and Hill, 1988). Some cancers (uterus, ovary, or unknown) are associated with high endogenous melatonin levels, while others (liver, kidney, upper respiratory tract, breast, or skin) are associated with low levels (Tamarkin, 1982; Touitou et al., 1985).

Melatonin and Stress

The reported effects of stressors such as exercise, cold, noise, burns, or immobilization on melatonin levels are not uniform. Effects may vary among species and depending on duration of stress, preceding light exposure or fasted vs fed state (L'Hermite-Balériaux et al., 1986; Lynch and Deng, 1986; Tannenbaum et al., 1988). When stress increases melatonin levels, the mechanism of increased NAT activity sometimes differs from that seen with darkness. Darkness related increases are triggered by sympathetic input from the superior cervical ganglion. Some stress related increases appear to be caused by catecholamines released into the circulation by the adrenal glands. Removal of the superior cervical ganglion blocks light/dark effects on melatonin but does not change these stress responses. Adrenalectomy blocks some (but not all) types of stress effects on melatonin but does not alter light/dark effects (Lynch et al., 1977; Reiter and Troiani, 1987). Most often it appears that the increased circulating catecholamines seen during stress do not have pineal effects due to uptake of the catecholamines by presynaptic sympathetic nerve terminals in the pineal (Lewy, 1983a).

Interactions With Endocrine Systems

Melatonin shows complex interactions with other hormonal systems which are controlled by the hypothalamus. It may serve as a message of light information to these other systems (Reiter, 1986).

Growth Hormone

Melatonin's effects on growth hormone are complex. Melatonin has been reported to inhibit growth hormone response to various stimuli, including low blood glucose (Nordlund and Lerner, 1977; Miles and Philbrick, 1987). Melatonin administration alone has been reported to increase growth hormone levels markedly, an effect which is blocked by the opiate antagonist naloxone (Esposti et al., 1988). However, Weinberg et al. (1981) failed to find growth hormone effects with melatonin infusion. The nocturnal peak in growth hormone is lowered by sleep deprivation, and addition of bright light and/or melatonin infusion does not change this effect (Strassman et al., 1987).

Reproductive System

Many animals are seasonal breeders, and changes in light/dark cycle affect their reproductive systems. Exposing spring-summer breeding animals to short winter like photoperiods has an antigonadotropic effect. Syrian hamsters undergo regression of the reproductive system when maintained on short light periods (less than 12.5 hr of light per day). Appropriately timed pulses of light restore reproductive function (Brainard et al., 1986). Even a 10 second pulse of light administered 8 hours after lights off in hamsters living under a 6 hours light - 18 hours darkness cycle will maintain reproductive function (Earnest and Turek, 1984). The inhibitory effects of a short daily light period on hamster testicular function also are prevented by injections of the cholinergic agonist carbachol into the ventricles of the brain (simulating the effects of light on the SCN) if given at night but not when administered during day (Earnest and Turek, 1983). Effects of light/melatonin on the hamster gonadal system begin before birth. Tests involving melatonin infusions of pregnant pinealectomized hamsters indicate a limited period of prenatal sensitivity, starting close to and ending before birth (Weaver et al., 1987).

Administration of melatonin in the afternoon (probably simulating early darkness) during proestrus inhibited ovulation in the rat. This inhibition was overcome by injections of luteinizing hormone (LH) (Shao-Yao and Greep, 1973). Infusion pump administration of melatonin in the pattern of a given season in sensitive animals produces season-appropriate reproductive activity, regardless of the light/dark exposure (Arendt and Broadway, 1987). Similar to light, melatonin must have a pulsatile pattern to be effective. Continuously available melatonin blocks the usual antigonadotropic effects of the pineal gland in hamsters under restricted light conditions, probably by down-regulating melatonin receptors (Reiter et al., 1978, 1989).

The reproductive system also affects the melatonin system. Ovariectomy in rats causes elevated serum melatonin levels. Administration of estrogen and rogesterone to rats suppresses this rise in melatonin (Wurtman and Ozaki, 1978). Ovariectomy also markedly decreases the number of melatonin binding sites in the hypothalamus and medulla-pons, and binding is restored by estradiol injections (Zisapel, 1988).

There is evidence of light and melatonin effects on the human reproductive system as well. Ovarian activity (estradiol, progesterone, and testosterone levels) in women living in Oulu Finland is lower in autumn than spring. Oulu is located at 65°N and has 10 hrs daylight in September and October and 16 hours in March to May, so light-related seasonal variations might be exaggerated. This effect is independent from the ovarian suppression seen in competitive runners (Ronkainen et al., 1985). Daytime melatonin levels, the length of the nocturnal pulse and mean melatonin levels in 11 female subjects were all higher during winter (3-4 hours of light) than during summer (20-22 hours light). Estradiol and testosterone levels were depressed in winter and daytime LH and follicle-stimulating hormone (FSH) were elevated as was sex hormone-binding globulin (Kauppila et al., 1987). However, others have found highest melatonin levels in winter and summer, with lower levels in spring and fall (Arendt et al., 1979).

Melatonin infusion (125 mg/hr X 48 hr) significantly suppressed the normally high LH levels in 3 post menopausal women. It does not appear to act at a pituitary level so it may be modulating the secretion of hypothalamic gonadotropin releasing hormone (GnRH). The earlier finding of no effect of once a day intramuscular melatonin (Fideleff et al., 1976; Wright et al., 1986) may be due to the short half life (Aleem et al., 1984). The opiate antagonist naloxone elevates LH, and melatonin blocks this elevation (Esposti et al., 1988). Thus, melatonin's effects on the reproductive system may interact with or be mediated by the endogenous opiate system.

Progesterone, like melatonin, shows a nocturnal pulse of secretion (2 hours later for progesterone). In vitro studies of human ovaries indicate that melatonin (probably in supra-physiological doses) can stimulate progesterone synthesis in corpus lutea tissue from some stages of the menstrual cycle. (It is theorized that increased progesterone might then lead to ovarian suppression by negative feedback.) The mechanism by which melatonin increases progesterone is uncertain. Melatonin binding in the ovary (which would be expected if it was a direct effect) could not be demonstrated (MacPhee et al., 1975). However, melatonin levels in ovarian follicular fluid from women undergoing in vitro fertilization and embryo transfer were

found to be higher than serum levels, and animal studies have found that radioactive melatonin is concentrated by the ovaries (Reiter, 1988).

Waldhauser et al. (1984) studied children and found that daytime melatonin levels did not vary, but nocturnal levels decreased significantly both with sexual maturation and age. Nocturnal plasma concentrations of LH tended to vary inversely with those of melatonin. Zacharias and Wurtman (1964) reported that blind girls show earlier menarche, with earliest onset in those who had no light perception at all, again supporting the idea that light, perhaps via melatonin, has effects on the human reproductive system.

Adrenal Gland

Melatonin administration causes a decrease in adrenal size in mice. Pinealectomy causes adrenal gland enlargement and melatonin suppresses this hypertrophy (Vaughan et al., 1972). It has been suggested that melatonin depresses adrenal growth and corticosterone release indirectly via the hypothalamus. Plasma 17-hydroxycorticosteriod is depressed at night and increases at awakening (a pattern opposite to that of melatonin). The corticosteriod cycle shifts if the sleep period is shifted. Orth and Island (1969) showed that it also was altered if the light dark cycle was changed while holding sleep/wake times constant. Both light and sleep seemed to contribute, but light was more important. As the melatonin cycle can be shifted by alterations in the light/ dark cycle but does not shift if light/dark is held constant and wake/sleep is shifted (Vaughan et al., 1976), melatonin cannot be the only controller of corticosteroid rhythm. However, it may provide light related input to that system.

Others have found no effects of melatonin on corticosteroid synthesis or release. Findings regarding effects of corticosteroids on melatonin have been inconsistent, with disease states involving high serum corticosteroids associated with normal, high and low melatonin levels. Evening administration of the corticosteriod dexamethasone depressed nocturnal melatonin in adults but increased it in prepubertal children (Demisch et al., 1987, Lang and Sizonenko, 1988).

Thyroid Gland

Endogenous melatonin and cyclically administered exogenous melatonin appear to depress thyroid function in animals (Paccotti et al., 1988). Constantly elevated melatonin (e.g. subcutaneous pellets) has a stimulatory effect on thyroid hormone. Thyroid releasing hormone originates in the area of the PVN of the hypothalamus (Vriend and Steiner, 1988) which is part of the melatonin control system. Thyroid hormone may have a mild stimulatory effect on melatonin production (Nir, 1978; Vriend and Steiner, 1988).

Prolactin

There is little evidence of any interaction of the melatonin system with prolactin release. Plasma levels of prolactin increase during night. This increase is lowered by sleep deprivation. Presence or absence of bright light and/or melatonin infusion during sleep deprivation has no effect (Strassman et al., 1987; Byerley et al., 1988). Paccotti et al. (1988) found that high (100 mg) or low (1 mg) doses of melatonin administered in morning or evening had no effect on prolactin response to exogenous gonadotropin-releasing hormone. Chronic oral administration of 2 mg melatonin at 1700 shifted prolactin rhythm to an earlier morning decline, but overall levels were unchanged (Arendt et al., 1987).

In summary, the relationship of the melatonin cycle to other endocrine systems is complex. One cannot say simply that melatonin suppresses this system or stimulates that one. The most consistent effect is suppression of the reproductive system, but even here, correctly timed infusions can have stimulatory effects. Under normal physiological circumstances melatonin probably transmits information about light exposure to these systems (Reiter, 1986). When it is administered in pharmacological doses this relationship may be changed. The pattern of administration more important than the dose. This will be discussed further under the section on exogenous melatonin.

Melatonin and Medical Diseases or Syndromes

A number of medical syndromes are associated with melatonin abnormalities. Diseases with associated decreased norepinephrine release, such as primary

degeneration of the autonomic nervous system or diabetic autonomic neuropathy show decreased nocturnal melatonin (Checkley and Palazidou, 1988). Klinefelter's syndrome, Turners syndrome, psoriasis vulgaris, spina bifida occulta, and sarcoidosis, all show loss of the melatonin circadian rhythm, with psoriasis vulgaris, spina bifida occulta, and sarcoidosis showing very high levels. Cortisone treatment in sarcoidosis increases melatonin levels even further (Miles and Philbrick, 1987).

As was mentioned previously, Touitou et al. (1985) found that certain cancers are associated with high or low levels of melatonin. Additionally, they reported that renal failure (the kidney is involved in the metabolism of melatonin), inflammatory syndrome, heart disease and diabetes were associated with high plasma melatonin levels, while neurological disease and alcohol and/or tobacco addiction were associated with low levels. These associations occurred predominantly in females, except for alcoholism which was associated with changed levels only in males. Alzheimer's disease is associated with lower melatonin levels than age matched controls (Nair et al., 1986b).

Effects of Exogenous Melatonin

It must be stressed that timing and pattern of melatonin administration are more important than the dose in affecting physiological parameters. The same dose given at different times or in different patterns can have different effects. The main result of continuous melatonin administration appears to be obliteration of all effects of endogenous and exogenous melatonin and perhaps light, probably by down-regulation of melatonin receptors. Pulsatile administration during sensitive periods is necessary for most effects (Reiter, 1989).

Sleepiness

The psychopharmacological effects of oral, intranasal (avoids first pass hepatic metabolism) or intravenous melatonin are similar to those of sedative hypnotics (Wright et al., 1986; Miles and Philbrick, 1988). Doses which have been given to humans range up to 6.6 grams a day for 35 days (Lerner and Nordlund, 1978). Even a 2 mg dose creates transient plasma

levels 10 to 100 times the normal range (Borbély, 1986) so any extrapolations about physiological effects of endogenous melatonin must be made cautiously. Patients given 250 mg melatonin by mouth four times a day for 25-30 days as an experimental treatment for hyperpigmentation reported drowsiness initially, which decreased as the study progressed (Nordlund and Lerner, 1977).

Sleep-inducing effects of melatonin might be indirect via arginine vasotocin, a sleep-inducing pineal hormone for which melatonin is a releasing hormone (Pavel, 1978). Whatever the mechanism, sleepiness following melatonin administration is transient, with the effect dissipating even before blood levels fall (Lieberman et al., 1984). However, a high dose (100 mg) was found to cause sleepiness persisting for a few hours with both morning and evening administration (Paccotti et al., 1988).

Performance

Melatonin 240 mg (administered in 3 doses 2 hours apart) caused a slowing of four-choice reaction time, with a decrease in errors of commission on both four-choice and simple reaction time tasks. The authors explain this as a result of the speed/accuracy relationship (speed is inversely related to accuracy so slowing subjects down made them more accurate). They differentiate this from errors of omission, the type of error most sensitive to fatigue. Errors of omission did not change with melatonin administration. Sustained complex motor performance (grooved pegboard test), digit symbol substitution, critical flicker fusion, and memory (both recall and recognition) were unaffected by melatonin (Lieberman et al., 1984).

Temperature

Melatonin administration causes decreased body temperature in some mammals (Ralph et al., 1979), although it elevates the temperature of rats. Intranasal inhalation is sometimes associated with shivering (Armstrong et al., 1986).

Entrainment of Circadian Rhythms

Studies have shown evidence that exogenous melatonin can entrain or shift the endogenous melatonin cycle (Armstrong et al., 1986; Mallo et al., 1987).

A phase response curve to this effect has been reported (Arendt, 1988) which appears to relate to fluctuations in melatonin binding sites or receptors in the hypothalamus and perhaps other areas of the brain (Zisapel, 1988). The possibility that melatonin could be used to reset the melatonin clock prompted its trial as prophylaxis against jet lag. Arendt et al. (1986) reported that melatonin significantly reduced jet lag after an eastward flight across 8 time zones as compared to placebo. Their subjects took 5 mg per day orally at 1800 hr local time for 3 days before the trip and continued the same dose (2200 to 2400 local time) through 4 days after traveling. Those who received melatonin treatment also showed shorter sleep latency, improved sleep quality (Arendt et al., 1987), and more rapid synchronization of melatonin and cortisol to the new time zone (Arendt, 1988). There are plans to market melatonin pills as a treatment for jet lag (Seligmann and Robinson, 1989). However, phase shifting with melatonin remains a controversial question. Wever (1986), also using a 5 mg dose, found no significant effect on entrainment of circadian rhythms after shifts under controlled laboratory circumstances. Armstrong and Chesworth, (1987) found that melatonin could phase shift free-running rats only when administered in a brief period during the early evening.

Adverse Effects

Extensive screening in studies of melatonin administration in humans has revealed no evidence of significant detrimental effects (Nordlund and Lerner, 1977; Wright et al., 1986), although high doses may cause headache and/or abdominal cramps, as is sometimes seen with its precursor amino acid, tryptophan (Lerner and Nordlund, 1978). Pathologically depressed patients sometimes become worse when given melatonin (Carman et al., 1976).

Pharmacological Agents which Affect the Melatonin System

Adrenergic Agonists and Antagonists

As was discussed previously, beta-adrenergic receptor antagonists such as propranolol can block melatonin production by preventing norepinephrine release from the SCG from affecting the pineal. One would expect beta-adrenergic receptor agonists to increase melatonin release. This is true in rats, but so far has not been demonstrated in humans. The response of rat

pineal gland to beta-adrenergic receptor stimulation is decreased if there has been a preceding high level of stimulation, and increased if there has been a period of no stimulation (Zatz, 1978). In hamsters, the pineal only responds to beta-receptor agonists late in the dark period (the time of the usual endogenous melatonin peak). It is theorized that similar limitations may explain lack of response of the human pineal to these drugs, as most such experiments have been performed in day time (Reiter, 1989). One group reported no effects with nocturnal administration in women; however, they used a $beta_2$-agonist, not a $beta_1$-agonist (Sizonenko and Lang, 1989).

Administration of clonidine (central $alpha_2$-agonist) decreases nocturnal melatonin while administration of the selective $alpha_2$-antagonist idozoxan increases it (Pelayo, et al., 1977; Levy et al., 1986; Grasby et al., 1988). This presumably is mediated by effects on the presynaptic inhibitory $alpha_2$ receptors of the SCG terminals in the pineal.

Opiate Agonists and Antagonists

Mu-type opiate receptor blockers such as naltrexone prevent melatonin immunity augmentation effects. Melatonin administration is reported to markedly increase growth hormone levels, an effect which is blocked by the opiate antagonist naloxone. Naloxone also decreases serum melatonin levels and blocks the nocturnal pulse (Esposti, 1988), while morning administration of an endogenous opiate to 5 psychiatric patients resulted in a marked increase in urinary melatonin output (Touitou et al., 1987). Thus, opiates apparently are involved not only in effects but also production of melatonin.

Prostoglandin Synthesis Inhibitors

Prostaglandins also appear to be involved in melatonin control. In rats, indomethacin, an inhibiter of prostaglandin synthesis, decreases melatonin levels. In humans, administration of ibuprofen, another drug which blocks prostaglandin synthesis, reduces melatonin levels proportionally to plasma concentrations of drug. Early evening administration delays the nocturnal pulse and slow release ibuprofen can block completely the nocturnal rise (Bird et al., 1986; Surrall et al., 1987). Data suggest that the effect is at the level of the pineal rather than the oscillator (Surrall et al.,

1987). Therefore, drugs which inhibit prostaglandin synthesis would not be expected to cause phase shifts, just acute suppression.

Benzodiazepines

Melatonin binds strongly to brain benzodiazepine receptors (Touitou et al., 1987). The benzodiazepine triazolam can phase shift or entrain melatonin rhythms in free-running hamsters (constant light, constant dark, or blind). The phase response curve is quite different from that of light. Triazolam causes phase advances at times when light has no effect and phase delays at times when light causes an advance (Turek and Losee-Olson, 1986; Van Reeth and Turek, 1989). It has been suggested that this might be mediated by effects on GABA-containing neurons in the hypothalamus. However, triazolam causes increased activity in hamsters (which are nocturnal animals), and blocking this activity by immobilizing animals prevents phase shift effects (Van Reeth and Turek, 1989). So effects may be indirect via stimulation of exercise rather than direct.

Indeed, stimulation of activity by non-drug techniques has been shown to speed adjustment of hamsters subjected to an 8 hour phase advance (Mrosovsky and Salmon, 1987). Reebs and Mrosovsky (1989) reported that free running (constant dark) hamsters show a phase-response curve to induced wheel running, with phase advances during the second half of the sleep period and phase delays during the late wake period and early sleep period. Most phase shifts were small and not all animals responded, so this was termed a weak zietgieber. Phase shifting effects of physical activity in humans have not been reported. Weinberg et al. (1979) found that keeping young men at bed rest in a fixed light/dark cycle had no effect on mean daytime or nocturnal melatonin as compared to levels seen with usual daily activities. Strenuous activities were not discussed in that report.

Bedtime administration of triazolam in humans has no major effects on melatonin (L'Hermite-Balériaux et al., 1987). This would have been predicted based on the phase-response curve seen in hamsters. A single evening dose in humans of another benzodiazepine, alprazolam, caused no significant change in melatonin at a dose of 0.5 mg, but caused marked depression of melatonin levels at a dose of 2 mg. The suppression persisted from 2 hours

after administration through the rest of the night. A preliminary report of effects of some other benzodiazepines on melatonin in humans was inconclusive (Touitou et al., 1987). Administration of diazepam blocked light induced phase advances in activity rhythms of hamsters but did not affect phase delays. Administered without light the drug caused small phase delays (Ralph and Menaker, 1987).

Melatonin Analogs and Antagonists

Melatonin analogs and antagonists can serve as useful research tools to further define the role of melatonin in physiological processes; and, these compounds may have important therapeutic potential in pathological conditions. The discovery that melatonin and related agonists selectively inhibited [^{3}H] dopamine release from retinal tissues permitted quantitative determination of their relative potencies (Dubocovich, 1983). The more potent agonists were found to possess a methoxy group on carbon 5 of the indole nucleus and an N-acetyl group on the same position as melatonin (Dubocovich, 1985). Accordingly, the most potent agonists were 5-methyl-N-acetyl-tryptamines, such as 2-iodomelatonin and 6,7-dichloro-2-methyl-melatonin, which possessed approximately four and eight times the potency to inhibit dopamine release, respectively, compared to melatonin (Dubocovich et al., 1986; Dubocovich and Takahashi, 1987). Some analogs are much more potent and have longer duration of action than melatonin itself (Clemens and Flaugh, 1986).

In contrast, the N-acetyltryptamines lacking the 5-methoxy group showed melatonin-receptor antagonist activity. The most potent and selective of this class evaluated to date is luzindole (N-0774; 2-benzyl-N-acetyltryptamine), which is an N-acetyltryptamine that lacks the 5-methoxy group, but possesses a 2-benzyl substitution. It has been shown previously that [^{3}H] dopamine release can be inhibited by the dopamine agonist apomorphine (Dubocovich and Weiner, 1981 and 1985), opiate agonists (Dubocovich and Weiner, 1983), the alpha-2 adrenergic agonist clonidine (Dubocovich, 1983), and melatonin (Dubocovich, 1983 and 1984). Tested at 1mM, luzindole completely antagonized the melatonin-induced inhibition of [^{3}H] dopamine release in a competitive manner. Using the agonists, 6-chloromelatonin and 6,7-dichloro-2-methyl-melatonin, yielded results similar to those obtained

with melatonin (Dubocovich, 1988a). The fact that luzindole is a selective melatonin antagonist is supported by the finding that a 1mM concentration, which is highly effective in inhibiting the effects of melatonin, did not modify the inhibition of dopamine release mediated by the dopamine agonists, apomorphine, or clonidine (Dubocovich, 1988b). Furthermore, luzindole, in concentrations ranging from 1nM to 100 mM, had no effect on the binding of specific radioligands to brain membrane receptors, including alpha-1 and alpha-2 adrenergic, beta-1 and beta-2 adrenergic, D-1 and D-2 dopaminergic, serotonergic 5 HT-1 and 5 HT-2, muscarinic, adenosine-1 or benzodiazepine receptors (Dubocovich, 1988a). The melatonin receptor blocking activity of this highly selective, potent, competitive melatonin-antagonist has been confirmed by in vivo studies (Fang and Dubocovich, 1988a and 1988b). Behavioral tests in animals suggest that luzindole also has antidepressant activity. This effect was more pronounced at midnight, when melatonin levels are elevated. Therefore, it is likely that luzindole's antidepressant activity in the behavioral despair test was mediated by blocking effects of endogenous melatonin in the brain (Mogilnicka and Dubocovich, 1987).

Other Agents

Early afternoon administration of tetrahydrocannabinol, a derivative of marijuana, caused large increases in plasma melatonin 2 hours later. Acute and chronic administration of 8-methoxypsoralen, a drug used in psoriasis, increases melatonin, especially with evening administration. This drug also prevents suppression of melatonin by bright light (Touitou et al., 1987). No effects on sleep or other circadian factors are described for methoxypsoralen in the Physicians' Desk Reference (1989).

Conclusion and Possible Future Research

Melatonin plays an important role in regulating neuroendocrine functions. Light and the melatonin cycle are critical factors in control and adjustment of the body's circadian rhythms. There are many possible investigations of military relevance related to melatonin.

The brightness-wavelength-duration characteristics of a light stimulus versus its effects on melatonin need to be better defined. If light exposure of specific brightness and duration has a given effect, does a light which is half as bright but lasts twice as long, administered at the same point in the phase response curve have the same effect? The possibility of direct effects of darkness is unresolved. Do activity pattern changes seen in constant-light hamsters subjected to dark pulses (Ellis et al., 1982; Harrington and Rusak, 1986) reflect melatonin changes? Are there similar effects in humans? Can dark pulses (longer than 2 hours) imposed on the light period of a usual light dark cycle cause shifts? If so how dark does it have to be, and does the degree of darkness required vary depending on the light level a person is accustomed to? Is there a brightness-duration trade off in darkness? If a short period of total darkness can cause a shift, how about a longer period of very low level light? Defining these features might allow development of patterns of light and dark exposure which are powerful circadian phase shifters.

It is possible that use of bright light exposure in SAD and other mood disorders could have implications for mood problems and insomnia suffered people living in areas subject to seasons with very short periods of daylight. However, various studies indicate differences in patients with depression as compared to normals in circadian factors and response to light. Thus, one must be careful in drawing general conclusions about the melatonin system based on SAD studies. Previous studies of light treatment in men working in the Antarctic during winter (Broadway et al., 1987) showed no benefit on mood or performance. However, that study used light in both morning and evening, did not control or record other light exposure and did not take into account endogenous circadian cycles (e.g. temperature rhythm) of the individual subjects in timing of intervention. These factors may explain the negative findings. Another possible treatment for winter mood problems might be an antidepressant melatonin antagonist.

The use of carefully timed light exposure to prevent or decrease jet lag also could have military applications. The dramatic phase shifting effects of bright light on body temperature (Czeisler et al., 1989) need to be confirmed in studies which also include melatonin and performance measure-

ments. Research will be required to determine the feasibility and effectiveness of causing circadian phase shifts with bright light before, during or after transporting military personnel across time zones. The possibility of building up larger shifts by sequential light exposures in the same circadian cycle also deserves investigation (Pittendrigh, 1988). Because timing of light in relation to each individual's circadian phase appears to be so important, the bright light mask which is being developed (Kripke and Cole, 1989) may be useful, especially if this mask allows effective administration of bright light during sleep.

Melatonin has been proposed as a prophylactic treatment for jet lag. Studies are needed to determine how much of a phase shift can be triggered with exogenous melatonin. Even if it proves too weak as a single agent, it might be useful in combination with light exposure, perhaps taking advantage of its sedative effects to help trigger sleep at an appropriate time for the target time zone. We have found no reports of combining controlled bright light exposure and exogenous melatonin. Another substance that might be used in addition is the melatonin precursor tryptophan, which shows evidence of being a sleep promoting agent (Spinweber and Johnson, 1983). Melatonin receptor antagonists may cause circadian phase shifts as well. Thus far there has been no investigation of this.

Phase shifting effects of benzodiazepines not well defined. Reports of various different benzodiazepines have not presented consistent effects. Further investigation would be wise before implementing these drugs in military settings, since such agents have detrimental effects on performance for several hours after administration and may cause anterograde amnesia (Spinweber and Johnson, 1983).

A number of chronically prescribed drugs have effects on the melatonin system. Clonidine and beta-adrenergic receptor antagonists commonly are used to treat hypertension. Non-steroidal anti-inflamatory agents, which inhibit prostaglandin synthesis often are used in various types of arthritis and also to treat acute pain syndromes. What are the sequela on an individual's circadian rhythms when melatonin release is chronically suppressed at the pineal level? Other zeitgebers probably would keep such people from 'free

running', but their circadian rhythmicity might be established less strongly than normal. Clonidine occasionally can cause insomnia, consistent with its effects on melatonin. However, it more often causes sedation (Rudd and Blaschke, 1985), probably related to effects on parts of the brain other than the pineal.

It is very likely that chronic suppression of melatonin causes melatonin receptors to up-regulate, as other types of receptors do under circumstances of lack of agonist (Motulsky and Insel, 1982), making the individual super-sensitive to any endogenous or exogenous melatonin (this question would require animal studies). In the reverse situation (chronic administration of melatonin, a melatonin agonist, or perhaps an antidepressant that caused long-term melatonin elevation) down-regulation of receptors may occur.

Looking at acute rather than chronic use of melatonin suppressing drugs, one interesting area for investigation would be the use of a non-steroidal anti-inflamatory agent like ibuprofen to suppress the melatonin peak during a period of night work, particularly during a sustained operation. Exogenous melatonin causes sleepiness, endogenous melatonin levels are correlated with sleepiness and the levels of melatonin in the blood increase during sleep deprivation (Åkerstedt et al, 1979). While there are monotonic decrements in performance and increases in fatigue over prolonged sustained operations, by far the most dramatic deteriorations occur around the time of the circadian peak in melatonin. Thus, it seems possible that acutely suppressing melatonin during the period of the usual peak could decrease the mood and performance decrements usually seen during the peak. Such agents could be used in conjunction with actual stimulants.

Like clonidine, non-steroidal anti-inflamatory agents infrequently cause both increased and decreased sleepiness (Physician's Desk Reference, 1989). However, administration only at night during sleep deprivation has not been investigated. The tendency for beta blocking drugs to cause feelings of fatigue and to decrease aerobic performance would overbalance benefits from suppression of melatonin, so they could not be recommended for this purpose. Melatonin antagonists might also be useful for this sort of application, as

might bright light. The use of bright light under night shift work conditions is currently under investigation at the Naval Health Research Center, in collaboration with the San Diego VA Medical Center and the University of California, San Diego.

Possible phase shifting effects of physical exercise should also be investigated. Presumably, if there are effects there would be a phase response curve, so exercise at different times of day and night would have to be tested. Such studies would require careful control of light exposure to differentiate the effects and possible interactions of exercise and light on melatonin.

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The control system for and effects of the hormone melatonin are discussed. The importance of light to human circadian rhythms is reviewed. Known and theoretical interventions which might be used to alter melatonin and other circadian variants are discussed.

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